EXHIBIT 12

Epilepsia, **39**(7):793–798, 1998
Lippincott–Raven Publishers, Philadelphia

Special Article

A North American Registry for Epilepsy and Pregnancy, a Unique Public/Private Partnership of Health Surveillance

The North American Pregnancy and Epilepsy Registry*

Summary: *Purpose:* A North American Registry of Epilepsy and Pregnancy (NAREP) has been established as a surveillance mechanism to identify adverse pregnancy outcomes that may be associated with fetal exposure to antiepileptic drugs (AEDs). As public attitudes become more receptive, and medical management more effective, women with epilepsy (WWE), are choosing to become pregnant in increasingly larger numbers. In the United States alone, 800,000 to 1.1 million WWE are of childbearing age. The offspring of these women have rates of congenital malformations of 1.25–11.5%. Although several factors could contribute to this risk, including AEDs, seizures during gestation, and maternal epilepsy, AEDs are an important variable over which we have some control. Unfortunately, no data currently exist that permit physicians to determine the relative safety of specific AEDs. With the introduction of several new AEDs, there is even further uncertainty about the potential safety of AEDs for treatment of pregnant women.

Methods: We have organized a prospective registry for pregnant WWE which will systematically monitor pregnancy outcomes. The registry can serve as an early warning system for adverse outcomes associated with specific AEDs, administered alone or in combination. The registry has required a cooperative effort between the scientific and pharmaceutical communities. The genesis of this effort is described. **Key Words:** North American Registry of Epilepsy and Pregnancy—Antiepileptic drugs—Pregnancy outcome—Drug safety.

BACKGROUND

The overall prevalence of epilepsy is 0.6–1.0% (1), and there are an estimated 800,000–1.1 million women with epilepsy (WWE) of childbearing age in the United States alone. These women are at risk for a variety of adverse pregnancy outcomes: worsening of seizure frequency, alterations in the metabolism of AEDs, fetal death, congenital malformations, congenital anomalies, and developmental delay.

WWE are unique in that their condition necessitates the use of antiepileptic drugs (AEDs). Without AEDs, these women are at increased risk for seizures, personal injury, loss of employment or driving privileges, and sudden unexplained death in epilepsy (SUDEP). Convulsions are undesirable during pregnancy. First-trimester seizures result in a risk of 12.3% of congenital malformations in the offspring as compared with a risk of 4% in children exposed to maternal seizures at other times (2). Generalized tonic-clonic seizures (GTCS) place both mother and fetus at risk for hypoxia and acidosis (3). Stillbirths have occurred rarely after a single generalized convulsion (4,5) or series of seizures (6). Status epilepticus (SE) carries a high mortality rate for mother and fetus. Teramo and Hiilesmaa (7) reported SE to be an uncommon complication of epileptic pregnancies. Yet of the 29 reported cases, 9 of the mothers and 14 of the infants died during or soon after an episode of SE. Generalized (although not partial) seizures occurring during labor can have a profound effect on fetal heart rate (8), and an increased rate of neonatal hypoxia and low Apgar scores among infants of WWE may be related to such events (9).

The potential problems related to seizures in pregnant WWE means that most such women will continue treatment with AEDs. However, AEDs are associated with an increased risk of congenital malformations, congenital anomalies, neonatal hemorrhage, feeding difficulty, and developmental delay (Table 1).

Several potential factors could account for the two- to threefold increased rates of malformations in infants of mothers with epilepsy (IME), including maternal seizures during pregnancy, potential genetic factors related to epilepsy, falls and injuries from seizures, and lower socioeconomic status, which may be associated with limited access to prenatal care. However, a series of observations strongly implicates AEDs as the major cause of

Accepted March 18, 1998.

* Comprised of the Scientific Advisory Board: Mark S. Yerby (Chair), J. F. Annegers, Joseph Bruni, Janet Cragan, Lewis Holmes, Margaret Jacobs, and Robert Mittendorf; and the Steering Committee: The Scientific Advisory Board, plus Nancy Brandenburg, Mike Carroll, Daniel Fife, Lisa Ford, Marc Kamin, Faye Luscomb, Azmi Nabulsi, and Patricia Tennis.

Address correspondence and reprint requests to Dr. M. S. Yerby at Oregon Comprehensive Epilepsy Program, Oregon Health Science University, 2455 Northwest Marshall, Suite 14, Portland, OR 97210, U.S.A.

TABLE 1. *Teratogenicity of AEDs: Malformation rates in the offspring of epileptic and control mothers*

Reference	Control		Epileptic mothers	
	Malformation rate (%)	No. of pregnancies	Malformation rate (%)	No. of pregnancies
Sabin and Oxorn (11)			5.4	56
Janz and Fuchs (12)			2.3	225
German et al. (13)			5.3	243
Elshove and Van Eck (14)	1.9	12,051	15.0	65
Speidel and Meadow (15)	1.6	483	5.2	427
South (16)	2.4	7,892	6.4	31
Spellacy (17)		50	5.8	51
Bjerkedal and Bahna (18)	2.2	12,530	4.5	311
Fedrick (19)	5.6	649	13.8	217
Koppe et al. (20)	2.9	12,455	6.6	197
Kuenssberg and Knox (21)	3.0	14,668	10.0	48
Lowe (22)	2.7	31,877	5.0	245
Meyer (23)	2.7	110	18.6	593
Millar and Nevin (24)	3.8	32,227	6.4	110
Monson et al. (25)	2.4	50,591	4.7	306
Miswander and Wertelecki (26)	2.7	347,097	4.1	413
Biale et al. (27)			16.0	56
Knight and Rhind (28)	3.65	69,000	4.3	140
Starreveld and Zimmerman (29)			7.0	372
Visser et al. (30)	2.3	9,869	3.7	54
Weber et al. (31)	2.2	5,011	4.0	731
Annegers et al. (32)	3.5	748	8.1	259
Seino and Miyokosh (33)			13.7	272
Dieterich et al. (34)				37
Majewski et al. (35)			16.0	111
Nakane et al. (36)			11.5	700
Hiilesmaa et al. (37)	2.0	5,613	7.7	4,795
Lindhout et al. (38)			2.4	151
Stanley et al. (39)	3.4	62,265	3.7	244
Beaussart et al. (40)			7.8	295
Kallen (41)			4.9	635
Robert et al. (42)	1.4	20,916	6.7	148
Rating et al. (43)	3.7	162	5.3	150
Gaily (44)	2.9	105	9.1	153
Dravet et al. (45)	1.4	117,183	7.0	281
Kaneko et al. (46)			6.2	145
Koch et al. (47)	4.3	116	6.9	116
Lindhout et al. (2)			7.6	172
Tanganelli and Regesta (48)	2.6	140	3.6	138

AEDs, antiepileptic drugs.

teratogenicity. First, comparisons of malformation rates in the offspring of mothers with epilepsy treated with AEDs as compared with those whose mothers received no AED treatment show consistently higher rates of malformations in the children of the treated group (Table 2) (15,16,22,25,32,36). Second, mean plasma AED concentrations are higher in mothers with malformed infants than in mothers with healthy children (51). Third, IME exposed to polytherapy have higher malformation rates than those exposed to monotherapy (38,50). Finally, in most studies, maternal seizures during pregnancy do not appear to increase the risk of congenital malformations (19).

Although polytherapy probably carries more inherent risks than monotherapy, high drug levels and multiple drugs may reflect the severity of epilepsy. Seizure frequency or severity may therefore be a confounding factor, and AEDs may be only associated with, not causally responsible for, malformations. Majewski et al. (35) described increased malformation rates and CNS injury in IME exposed to maternal seizures. More recently, Lindhout et al. (2) described a marked increase in malformations in infants whose mothers had seizures in the first trimester: 12.3 versus 4.0%. Most other investigators, however, have not reported a relationship between maternal seizures during pregnancy and the frequency of malformations, development of epilepsy in the offspring, or febrile convulsions (32,36).

A major issue in evaluating the relationship between maternal epilepsy and congenital malformations is whether the association is confounded by potential genetic factors related to the mother's epilepsy. Few investigators have compared malformation rates in groups of treated and untreated mothers with epilepsy.

Data to differentiate among established AEDs in terms of safety are not avaliable. The introduction of five new

AEDs in North America (gabapentin, felbamate, lamotrigine, tiagabine and topiramate), and several others on the horizon, further complicates therapeutic choices. Little is known about the possible teratogenic effects in humans of these new AEDs, whether used in monotherapy of in combination with other agents. In an editorial in *Lancet* (52), the states "... it is easy to be influenced by the flow of negative case-reports. Despite mounting evidence, the case remains to be proven ... by large prospective, multicenter and ideally international investigations based on pregnancy registers."

OBJECTIVES OF THE NORTH AMERICAN REGISTRY OF EPILEPSY AND PREGNANCY (NAREP)

The objective of the NAREP is to identify possible associations between fetal exposure to AEDs and adverse pregnancy outcomes. It will systematically monitor new AEDs and serve as an "early warning system" for patients and clinicians regarding potential problems with individual AEDs prescribed alone or in combination.

ORGANIZATION OF THE NAREP

The NAREP was conceived as being maintained by a center or organization (e.g., academic medical center, contract research organization, nonprofit organization). A senior scientist was recruited to administer the project by open solicitation for proposals based on guidelines established by a Scientific Advisory Board. A separate Steering Committee was organized to refine the protocol, manage the registry, and develop analysis.

The need for a registry was first discussed in December 1993, when a group of academic medical researchers and epidemiologists from several pharmaceutical companies that manufacture AEDs met informally. It was estimated that a prospective cohort epidemiological study of at least 2,000 WWE and a similar number of controls would be needed to identify specific risk factors for adverse pregnancy outcomes and to provide sufficient power to identify the differences among treatments after stratification was made by treatment type seizure type, and seizure frequency. The estimated cost of such a study (~$1 million) precluded initiating the project in 1993. A pregnancy registry was developed as a reasonable alternative and has the advantage of being a useful public health tool. Previous surveillance methods developed by epidemiologists at Burroughs-Wellcome provided useful models. The registry would be funded by a consortium of the pharmaceutical companies that manufacture AEDs.

TABLE 2. *Teratogenicity of AEDs: Malformation rates in the offspring of treated and nontreated epileptic mothers*

Reference	Malformation rate (%)	
	AEDs	AEDs
Janz and Fuchs (12)	2.2	0
Speidel and Meadow (15)	5.0	0
South (16)	9.0	0
Lowe (22)	6.7	2.7
Monson et al. (25)	5.3	2.9
Annegers et al. (49)	7.1	1.8
Annegers et al. (32)	10.7	2.4
Nakane (50)	11.5	2.3
Nakane et al. (36)	13.8	8.5
Robert et al. (42)	7.2	0
Rating et al. (43)	5.3	5.9
Koch et al. (47)	6.9	8.0

In meetings in the next 18 months, a surveillance mechanism was proposed and variables of interest were identified that allowed the structure of the registry to be formulated. The populations to be approached and mechanisms for so doing were determined. Methods for maintaining patient confidentially were discussed. Rules for maintaining the scientific integrity of the registry were established.

Requests for proposals incorporating the foregoing organizational issues were then advertised in major medical journals. Seven groups expressed interest, and six of these submitted proposals. The Scientific Advisory Board reviewed the proposals and selected the most competitive. A contract was then developed and an award was made to Dr. Lewis Holmes and his colleagues at the Massachusetts General Hospital in Boston, Massachusetts. The general structure of the NAREP is described in the following sections.

Scientific Advisory Committee

The NAREP is monitored and assisted by a Scientific Advisory Committee. This committee consists of academic medical researchers, none of whom have any financial interest in the pharmaceutical corporations. Currently, it consists of an epidemiologist (Dr. Fred Annegers), an obstetrician (Dr. Robert Mittendorf), a developmental pediatrician and representative of the Centers for Disease Control (Dr. Janet Cragen), a representative of the National Institutes of Health (NIH) Epilepsy Branch (Margaret Jacobs), a Canadian neurologist (Dr. Joseph Bruni), a neurologist-epileptologist (Dr. Mark Yerby), and the project's principal investigator (PI: Dr. Lewis Holmes, a teratologist).

The committee's charge is to advise and assist the PI in establishing and operating the Registry. This committee has final approval over the announcement and publication of registry data and conclusions to ensure that results are reported and interpreted accurately. Several variables are potentially confounding in determining associations among AEDs, seizures, and maternal epilepsy for pregnancy outcomes. Inaccuracies in reporting could have a profound impact on the health and choices of persons with epilepsy and on the viability of manufacturers. The committee can also act as a buffer between

the PI and the corporate financial supporters of the Registry if adverse outcomes are identified with a particular product.

The Steering Committee

The Steering Committee consists of the members of the Scientific Advisory Board plus representatives of the corporations that finance the Registry. The corporate representatives are epidemiologists and neurologists or representatives of medical affairs departments of their companies. The Steering Committee provides a link between each corporate sponsor and the Registry. It also advises the Registry on organizational and analytical issues relative to the project. Neither the Steering Committee nor the sponsoring corporations are permitted to actually analyze data or report outcomes. It has no control over the publication of findings or other reports from the Registry.

The sponsors

The following pharmaceutical corporations are providing a total of $50,000 each, annually, for each of the next 2 years to support the registry. Each also provides one representative to the Steering Committee. These sponsors were approached because they manufactured AEDs. All corporations manufacturing AEDs in North America (except Carter Wallace) have agreed to participate. They are:

Abbott Laboratories
Novartis
Glaxo-Wellcome
Hoechst Marion Roussel
Johnson & Johnson
Ortho-McNeil
Parke-Davis

Supporting organizations

Several other organizations are providing support by informing their constituencies about the Registry and encouraging WWE and their physicians to enroll.

American Epilepsy Society
Centers for Disease Control
Epilepsy Foundation of America
Epilepsy Branch of NINDS/NIH

Source populations

Initial surveillance will be limited to Canada and the United States. After enrollment in these countries is well established, the Registry will be extended to include Mexico and the United Kingdom. Target populations are (a) WWE with exposure to AEDs during pregnancy; (b) women without epilepsy with exposure to AEDs during pregnancy; and (c) WWE without exposure to any AED during pregnancy. The AED exposure interval of interest will be any time between the last menstrual period (LMP) and conclusion of the pregnancy.

Data collection

Potential subjects will be recruited directly by their physicians. Neurologists and obstetrician-gynecologists are the physicians most likely to treat such patients. These physicians will be encouraged to enroll all pregnant patients with epilepsy, as well as women without epilepsy who are treated with AEDs. Advertisements in professional journals, personal mailings, lectures, and information booths at national and regional meetings of appropriate professional societies will be the principle means of informing the medical community. Potential subjects will be recruited directly through announcements and articles in the newsletters of voluntary health organizations such as Epilepsy USA, the information hotline of the Epilepsy Foundation of America (EFA), and the Internet.

MECHANISM OF REPORTING

Reporting by patients

We anticipate that most pregnancies will be reported to the registry by the patients themselves, A toll free number (888-233-2334) has been established for accessing the Registry. At the time of the call, each patient will be sent an informed consent form, a registration form, and a card to inform the treating physicians (those who are supervising the epilepsy care or other indication for using an AED, as well as those supervising the pregnancy). The following data will be collected by the Registry.

- Age
- Race
- Physician supervising epilepsy
- Physician supervising pregnancy
- Physician supervising the condition for which AED is prescribed
- AED received since LMP, dose, and schedule
- LMP
- Expected date of confinement
- Family history of birth defects
- Seizures types and frequency
- Use of vitamin supplements before conception
- Use of vitamin supplements after conception
- Other exposures: alcohol, cigarettes, other medications

Confirmation of these data will be obtained from the treating physicians, who will also be informed that a follow-up interview will be performed 2 months after the anticipated date of delivery. Follow-up will involve both the patient and her physicians.

Reporting by physicians

Physicians can report potential subjects directly by calling 888-233-2334. After obtaining permission to contact the patient, the Registry will call the woman and

obtain consent and the same information described above.

Follow-up reporting

Two months after the expected date of delivery, a follow-up reporting form will be sent to the treating physicians, and a telephone interview will be conducted with the patient. The following data will be collected.

- Pregnancy outcome
- AED type, dose, and schedule
- Other exposures during pregnancy
- Infections/other medical conditions during pregnancy
- Seizure frequency during pregnancy

Outcomes of interest

If an adverse pregnancy outcome is determined or suspected, permission will be obtained to review pertinent hospital and medical records. The outcomes of interest are:

- Live birth without malformation
- Spontaneous abortion
- Induced abortion because of prenatal diagnosis
- Induced abortion without prenatal diagnosis
- Live birth with congenital malformations
- Maternal death
- Lost to follow-up

Data analysis and reporting

Descriptive data will be used to summarize the outcomes of interest. Drug- and seizure-specific incidence of birth defects will be calculated. Human teratogens tend to cause specific defects rather than increases in all types of malformations. The Registry will therefore seek clusters of specific defects or groups of defects. The distribution of specific defects or groups of defects will be compared between cohorts of women by AED exposure, seizure type, and frequency.

Confidentiality

All information that might be used to identify a specific individual will be kept strictly confidential. Outcomes will be reported by groups, without identification of individuals. Data about individuals will be made available only with the written consent of the patient, and only to individuals whom the patient identifies.

DISCUSSION

We believe that the NAREP represents a novel approach to utilizing academic expertise and private/corporate resources to develop and maintain an important public health project. WWE are faced with a dilemma when they consider pregnancy: medications are generally avoided by pregnant women, but without medication, WWE are at risk of seizures. Seizures themselves are associated with potential injury, miscarriage, and fetal death. At present, we lack information about the relative safety of specific AEDs or the relative risks of these AEDs as compared with risk of fetal exposure to maternal seizures. With the advent of new AEDs that have not been tested in pregnant women before being marketed, such issues become more acute.

Current surveillance mechanisms are voluntary and, because they are not population based, anecdotal. Because they do not permit calculation of prevalence estimates, they lack utility. Our goal is to improve this situation by designing a prospective, population-based Registry. There are three potential problems with such a Registry. First it must enroll a substantial proportion of the population of WWE if its prevalence figures are to be meaningful. Estimates of the number of persons necessary to distinguish among various medications in a classic case-control study are 2,000 in each group. An estimated 800,000 to 1.1 million WWE are of child bearing age in the United States and ~80,000–110,000 in Canada are of child bearing age. If we register 1% of such women, the data should be representative and thus can be extrapolated. Even 1% enrollment will require substantial effort.

Protection of subject identity is very important. Reporting will not identify persons as individuals. A risk remains, however: when telephone interview techniques are used, an individual could misrepresent himself or herself and thus obtain specific information about a person's epilepsy status. Interviewers must be cautious about revealing information by telephone.

We acknowledge a potential for conflict of interest and suppression of negative information about an AED. The Registry is supported financially by pharmaceutical corporations with a vested interest in promoting and selling their products. Adverse outcomes associated with a drug could result in a commercial disadvantage for its manufacturer. In addition, associations are not necessarily causal. Reporting must be accurate and balanced so that people with epilepsy are informed and protected but not misled or alarmed unnecessarily. The use of a Scientific Advisory Board as a buffer between the corporations (represented on the Steering Committee), and the PI will help reduce the potential for inadvertent or inappropriate influence by any particular company. Reports will also be submitted to peer-reviewed scientific journals, whose editorial and review process provides yet another layer of scrutiny.

Corporate sponsors who feared that an adverse outcome might be signaled prematurely had some understandable hesitancy about the establishment of the Registry. However, WWE are already treated with these drugs, and in the natural course of events some will become pregnant and a few of them may have adverse outcomes, whether or not the Registry exists. If a drug is shown to be associated with a higher than expected rate

of adverse outcomes, it could then be labeled more appropriately, the public warned, and corporate liability reduced. Concomitantly, studies could be designed to investigate the association and identify potential mechanisms. If a drug is shown not to be associated with an increased risk of adverse outcomes, the public can be so informed and the product can be used with a greater degree of safety. We believe that the Registry will provide significant benefit to the public, WWE, their offspring, and AED manufacturers.

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